UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,530	01/21/2004	Dwight D. Koeberl	01579-1155	3856

23117 7590 07/15/2010

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
07/15/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/761,530
Filing Date: January 21, 2004
Appellant(s): KOEBERL ET AL.

Mary J. Wilson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 06/14/10 appealing from the Final-Office action mailed 08/13/09.

(I) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(II) Related Appeal and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(III) Status of Claims

The statement of the status of claims contained in the brief is correct.

(IV) Status of Amendments After Final

The Appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(V) Summary of Claimed Subject Matter

The statement of the status of claims contained in the brief is correct.

For the purpose of this appeal, the claims on appeal shall stand or fall together.

(VI) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief (pages 16-20 of Appeal Brief dated 06/14/10) is correct.

(VII) Evidence Relied Upon

1. Van Bree et al., (WO 00/34451, 2000, in IDS);

2. Amalfitano et al., (WO 02/098466 A1, 2002, in IDS);

3. Heus JH (US Patent No.: 6,858,425 B1, claiming priority date of Application No.: 09/454,466 filed on 12/03/99);

4. Haseltine et al., (WO 2005/003296 A2, claiming priority date of Application No.: 60/441,305 filed on 01/22/03);

5. Martin et al., (WO 00/47741, 2000);

6. Whitfeld et al., (US Patent No.: 5,298,400, 1994); and

7. Meulien P (US Patent No.: 5,521,070, 1996)

8. Hoefsloot et al. EMBO J. 7,1697-1704 (1988) newly cited evidence reference.

(VIII) Grounds of Rejection to be reviewed on Appeal

The Appellants' statement of the grounds of rejection to be reviewed on appeal is substantially correct.

I. *Claim Rejections 35 USC § 102*

Claims 1, 2, 8-11, 18, 21, 22 and 24-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Bree et al., (WO 00/34451, 2000, in IDS) when given the broadest interpretation.

Claims 1, 2, 8-11, 18, 21, 22 and 24-29 are directed to any isolated nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to a human acid α-gluocosidase (GAA) polypeptide and comprising any secretory signal sequence including variants, mutants and recombinants, wherein said secretory signal sequence replaces the leader sequence of native human GAA and further comprising a polynucleotide from any 3' untranslated region, vector comprising said polynucleotides, host cell comprising said vector, a method of delivering said vector comprising said polynucleotide to a host cell and a method of expressing encoded polypeptide.

Van Bree et al., (*supra*) disclose compositions comprising polynucleotides encoding the human GAA with native secretory signal sequence and also suggest said GAA can be operably linked to other signal peptides (page 9, lines 16-30), vectors, methods of expression of encoded polypeptides, a method of expressing said polypeptide in many mammalian cultured cells such as CHO, 293 and methods to generate transgenic animals (*in vivo*) comprising polynucleotides encoding human GAA (Summary of the Invention: pages 3-28; especially pages 7, 9 and 10). In addition said reference teaches that: i) lysosomal proteins such as human GAA undergo proteolytic processing, in which the first event is removal of the signal polypeptide and renders the protein soluble (page 7, lines 26-32) and ii) the native secretion signal sequence (leader sequence) linked to the lysosomal protein coding sequence is replaced with a signal sequence that targets the processing enzyme to the endoplasmic reticulum (page 11, lines 29-35), providing evidence that the native leader sequence of human GAA can be replaced with any signal sequence of interest such as secretory signal sequence.

Additionally, examiner would like to point to the specific teaching in Van Bree et al., page 5, lines 26-29 which states "A DNA segment is operably linked when placed in a functional relationship with another DNA segment. For example, DNA for a signal sequence is operably linked to DNA encoding a polypeptide if it is expressed as a preprotein that participates in the **secretion** of the polypeptide". The evidence that replacing the leader sequence of native human GAA with a secretory signal sequence and demonstration of biological activities in said chimeric proteins were well known in the art and also envisaged by Van Bree et al., especially the native secretion signal

sequence (leader sequence) linked to the lysosomal protein coding sequence is replaced with a signal sequence that targets the processing enzyme to the endoplasmic reticulum (page 11, lines 29-35) or any signal sequence of interest such as mammary gland specific signal sequences/secretory signal sequence like α-lactalbumin, α-casein, β-casein that can be potentially employed as signal sequences for the expression of human GAA transgene, recovery of the expressed polypeptide and use of purified polypeptide for the treatment of patients having genetic or other deficiency resulting in insufficiency of functional lysosomal GAA enzyme (in pages 3-28; especially pages 7, 9 and 10 page 15; Example 3-4, pages 25-28). Thus, providing evidence that recombinant human GAA comprising heterologous secretion signals wherein native leader sequence has been replaced is correctly processed and biologically active, thus implying unaltered glycosylation and correct processing for the maintenance of biological activity.

Therefore, the reference of Van Bree et al., anticipates claims 1, 2, 8-11, 18, 21, 22 and 24-29 of the present invention.

II. *Claim Rejections 35 USC § 103*

Claims 5, 12, 14-16, 73, 75 and 80-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., (WO 00/34451, 2000, in IDS) as applied to claims 1, 2, 8-11, 18, 21, 22 and 24-29 above, and further in view of Amalfitano et al., (WO 02/098466 A1, 2002, in IDS).

Van Bree et al., (*supra*) disclose compositions comprising polynucleotides encoding the human GAA with native secretory signal sequence and also suggest said GAA can be operably linked to other signal peptides (page 9, lines 16-30), vectors,

methods of expression of encoded polypeptides, a method of expressing said polypeptide in many mammalian cultured cells such as CHO, 293 and methods to generate transgenic animals comprising polynucleotides encoding human GAA (Summary of the Invention: pages 3-28; especially pages 7, 9 and 10). In addition said reference teaches that: i) lysosomal proteins such as human GAA undergo proteolytic processing, in which the first event is removal of the signal polypeptide and renders the protein soluble (page 7, lines 26-32) and ii) the native secretion signal sequence (leader sequence) linked to the lysosomal protein coding sequence is replaced with a signal sequence that targets the processing enzyme to the endoplasmic reticulum (page 11, lines 29-35), providing evidence that the native leader sequence of human GAA can be replaced with any signal sequence of interest such as secretory signal sequence.

However, Van Bree et al., (*supra*) are silent regarding said polynucleotide encoding the human GAA is operably linked to transcriptional control element operable in liver cells (as in claim 5), wherein the vector is an adeno-associated virus (AAV) vector (as in claims 12), a pharmaceutical composition comprising said polynucleotide and vector (as in claims14-16, and 80-82), said polynucleotide encodes the amino acid residues 28-952 of SEQ ID NO: 2 (as in claims 73 in part and 75).

Amalfitano et al., (*supra*) teach adenovirus and adeno-associated virus vectors comprising polynucleotides encoding chimeric polypeptides comprising a secretory signal sequence operably linked to human GAA including the amino acid residues 28-952 of SEQ ID NO: 2 (lines 13-26, page 22) and a method of producing said polypeptide in many mammalian cultured cells such as CHO, 293 and *in vivo* in

hepatocytes (Summary of the Invention: pages 3-41; especially pages 6, 7, 12, 22, 26, 28-30, 35, 41 and Examples 1, 4, 9, and 13), and pharmaceutical compositions comprising said polynucleotides and vector (entire document).

Therefore, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Van Bree et al., and Amalfitano et al., to produce a polynucleotide configured in a suitable vector and encoding a therapeutic polypeptide composition comprising human acid alpha-glucosidase (GAA), said therapeutic polypeptide comprising any secretory signal sequence of interest that is suitable for targeting said polypeptide to any cell or tissue of interest depending on the clinical condition that need to be rectified. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and Golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport in the target tissues. The expectation of success is high, because Van Bree et al., disclose compositions comprising polynucleotides encoding the human acid alpha-glucosidase (GAA) with native secretory signal sequence and also suggest said GAA can be operably linked to other signal peptides (page 9, lines 16-30), vectors, methods of expression of encoded polypeptides, a method of expressing said polypeptide in many mammalian cultured cells such as CHO, 293 and methods to generate transgenic animals comprising polynucleotides encoding human GAA (Summary of the Invention: pages 3-28; especially pages 7, 9 and 10). In addition

said reference teaches that: i) lysosomal proteins such as human GAA undergo proteolytic processing, in which the first event is removal of the signal polypeptide and renders the protein soluble (page 7, lines 26-32) and ii) the native secretion signal sequence (leader sequence) linked to the lysosomal protein coding sequence is replaced with a signal sequence that targets the processing enzyme to appropriate sub-cellular compartments or tissue of interest. Similarly, Amalfitano et al., teach adenovirus and adeno-associated virus vectors comprising polynucleotides encoding chimeric polypeptides comprising a secretory signal sequence operably linked to human GAA including the amino acid residues 28-952 of SEQ ID NO: 2 (lines 13-26, page 22) and a method of producing said polypeptide in many mammalian cultured cells such as CHO, 293 and in vivo in hepatocytes (Summary of the Invention: pages 3-41; especially pages 6, 7, 12, 22, 26, 28-30, 35, 41 and Examples 1, 4, 9, and 13) and pharmaceutical compositions comprising said polynucleotides (entire document). Therefore, Claims 5, 12, 14-16, 73, 75 and 80-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., (WO 00/34451, 2000, in IDS) as applied to claims 1, 2, 8-11, 18, 21, 22 and 24-29 above, and further in view of Amalfitano et al., (WO 02/098466 A1, 2002, in IDS).

Claims 3, 4, 73, 75, 77, 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., (WO 00/34451, 2000, in IDS), Amalfitano et al., (WO 02/098466 A1, 2002, in IDS) and further in view of Heus JH (US Patent No.: 6,858,425 B1, claiming priority date of Application No.: 09/454,466 filed on 12/03/99) and

Haseltine et al., (WO 2005/003296 A2, claiming priority date of Application No.: 60/441,305 filed on 01/22/03).

Rejection of claims 1-2, 5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75 and 80-82 under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., and Amalfitano et al., is discussed above. Van Bree et al., and Amalfitano et al., teach isolated nucleic acids expressing lysosomal polypeptides as chimeric polypeptide comprising secretory signal sequence operably linked to human acid alpha-glucosidase (GAA), the full-length polypeptide, cleaved and mature forms of polypeptides including chimeric polypeptides comprising heterologous secretory signal sequences operably linked to said polypeptides. Van Bree et al., and Amalfitano et al., are silent regarding said polynucleotide comprising the 3' untranslated region of SEQ ID NO: 3 (as in claim 79) or said polynucleotide encoding a fusion polypeptide comprising SEQ ID NO: 5, an albumin signal peptide sequence (as in claims 5 and 73 in part).

Heus JH et al., have disclosed the human alpha glucosidase (GAA) gene, vector constructs and the 3' untranslated region sequence of said gene (entire document).

Haseltine et al., disclose the albumin signal peptide sequence of SEQ ID NO: 5 (as in claims 5 and 73 in part) and methods for fusing said signal peptide sequence linked to various therapeutic proteins as fusion proteins for use in gene therapy techniques.

Therefore, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Van Bree et al., Amalfitano et al., Heus JH., and Haseltine et al., to produce an isolated nucleic acid encoding a chimeric therapeutic polypeptide

such as human GAA comprising the 3' untranslated region of the human GAA polynucleotide sequence and further said encoded chimeric polypeptide comprising the albumin secretory signal peptide. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and Golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport in the target tissues. The expectation of success is high, because Van Bree et al., and Amalfitano et al., teach the use of lysosomal polypeptides such as human acid alpha-glucosidase (GAA) wherein leader sequence of native human GAA has been replaced with a heterologous secretory signal sequence, distinct advantages and the method of use of said polypeptide for therapeutic purposes and Heus JH., and Haseltine et al., teach the use of 3' untranslated region of the human GAA polynucleotide sequence and albumin secretory signal peptide as a chimeric polypeptide for effective targeting of said therapeutic polypeptides to clinically significant target tissues. Therefore, claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75, 77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., (WO 00/34451, 2000, in IDS) Amalfitano et al., (WO 02/098466 A1, 2002, in IDS) and further in view of Heus JH (US Patent No.: 6,858,425 B1, claiming priority date of Application No.: 09/454,466 filed on 12/03/99) and Haseltine et al., (WO 2005/003296 A2, claiming priority date of Application No.: 60/441,305 filed on 01/22/03).

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75, 77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., and further in view of Martin et al., (WO 00/47741, 2000).

Rejection of claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75, 77 and 79-82 as being unpatentable over Van Bree et al., Amalfitano et al., Heus JH and Haseltine et al., are described above. Said references do not specifically teach encoded chimeric polypeptide comprising an erythropoietin secretory signal sequence of SEQ ID NO: 6 linked to human GAA (as in claim 73 in part). Martin et al., specifically teach a therapeutic polypeptide comprising a native human erythropoietin signal peptide of SEQ ID NO: 6 (entire document).

It would have been obvious to a person of ordinary skill in the art to combine the teachings of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., and Martin et al., to produce a targeted therapeutic glycoprotein with a an erythropoietin secretory signal sequence (SEQ ID NO: 6) linked to therapeutic polypeptide GAA. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and Golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport to the target tissues of interest. The expectation of success is high, because Martin et al., teach the utility of therapeutic polypeptides comprising an erythropoietin secretory signal for effective

targeting of said therapeutic polypeptides to clinically significant target tissues. Therefore, claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75, 77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al.,), Amalfitano et al., Heus JH, Haseltine et al., and further in view of Martin et al., (WO 00/47741, 2000).

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., and further in view of Whitfeld et al., (US Patent No.: 5,298,400, 1994).

Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., and Martin et al., are described above. Said references do not specifically teach encoded chimeric polypeptide comprising a α-1-antitrypsin secretory signal sequence of SEQ ID NO: 8 linked to human GAA (as in claim 76 in part). Whitfeld et al., specifically teach a therapeutic polypeptide comprising a α-1-antitrypsin secretory signal sequence of SEQ ID NO: 8 (entire document).

It would have been obvious to a person of ordinary skill in the art to combine the teachings of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., and Whitfeld et al., to produce a targeted therapeutic glycoprotein with a an α-1-antitrypsin secretory signal sequence linked to therapeutic polypeptide GAA. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that

enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and Golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport to the target tissues. The expectation of success is high, because Whitfeld et al., teach the utility of therapeutic polypeptides comprising a α-1-antitrypsin secretory signal for effective targeting of said therapeutic polypeptides to clinically significant target tissues. Therefore, claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., and further in view of Whitfeld et al., (US Patent No.: 5,298,400, 1994).

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., Whitfeld et al., and further in view of Meulien P (US Patent No.: 5,521,070, 1996).

Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., and Martin et al., are described above. Said references do not specifically teach encoded chimeric polypeptide comprising a Factor IX secretory signal sequence of SEQ ID NO: 9 linked to human GAA (as in claim 76 in part). Meulien P specifically teaches a therapeutic polypeptide comprising a Factor IX secretory signal sequence of SEQ ID NO: 9 (entire document). It would have been obvious to a person of ordinary skill in the art to combine the teachings of Van Bree et al., Amalfitano et al., Heus JH, and Meulien P to produce a

targeted therapeutic glycoprotein with a Factor IX secretory signal sequence linked to therapeutic polypeptide GAA. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and Golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport to the target tissues. The expectation of success is high, because Meulien P et al., teach the utility of therapeutic polypeptides comprising a Factor IX secretory signal for effective targeting of said therapeutic polypeptides to clinically significant target tissues. Therefore, claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., Whitfeld et al., and further in view of Meulien P (US Patent No.: 5,521,070, 1996).

Therefore, the above references render claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 *prima facie* obvious to one of ordinary skill in the art.

(IX) Response to Argument

I. In support of their request for the rejection under 35 USC § 102 be withdrawn, Appellants' provide the following arguments:

(1) "Claim 1 (from which other claims subject to this rejection depend) relates to a nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to human GAA. It is submitted Van Bree et al., includes no such teaching…Appellants respectfully submit that Van Bree et al., does not "clearly and

unequivocally" disclose the claimed invention (or direct artisan to it) "without any need for picking, choosing and combining various disclosures not directly related to each other by the teachings of the cited reference" **(see pages 9-10 of Appellants' Appeal-Brief dated 06/14/10)**.

Reply (1): Appellants' arguments have been considered but are found to be non-persuasive for the following reasons:

The structural and functional elements of human acid α-glucosidase (GAA) are well known in the art. Said GAA comprisies a native signal sequence that targets the native human GAA to specific sub-cellular compartment such as endoplasmic reticulum, Goigi and lysosomes, where said signal sequence is cleaved following post-translational modification. It is also well recognized in the art, optimal heterologous or transgenic expression of human GAA requires that the native GAA signal sequence be replaced with the secretory signal sequence of interest for appropriate targeting of GAA or to be directed to appropriate secretory pathway for extracellualr secretion. This replacement of native signal sequence of human GAA with an heterologous secretory signal sequence is necessary to redirect the expressed transgenic product (GAA polypeptide) to achieve apporpriate tissue targeting or optimal secretion of the expressed polypeptide. The skilled artisan would also recognize that any heterologous tissue targeting or secretory signal sequence placed upstream of native human GAA signal peptide will result in cleavage of the heterologous targeting/secretory signal sequence along with the native human GAA signal sequence and appropriate targeting or optimal secretion of transgene will not be achieved and such a recombinant construct would

defeat the intended purpose of specifc targeting or optimal secretion of the expressed polypeptide. Hence, a skilled artisan will certainly be motivated to replace/delete the native signal sequence of human GAA to generate a transgenic construct comprising the appropriate heterologous targeting or seceretory signal sequence depending on the experimental need. Such strategies are envisaged in the reference of Van Bree et al., (WO 00/34451, 2000, in IDS). Examiner has re-produced below the relevant section of the reference of Van Bree et al., (WO 00/34451, 2000, in IDS) in addition to sections cited above in the rejection, as a ready reference that clearly and unequivocally provide evidence for replacing the native signal sequence of human GAA with a heterologous targeting or secretory signal sequence. Additionally examiner has also included the reference of Hoefsloot et al., (EMBO, 1988, Vol. 7 (6): 1697-1704), as Van Bree et al., (page 21, Example 1 of specification) describe the cDNA construct isolated by Hoefsloot et al. (provided herewith), and the use of said cDNA for the construction of Transgene, said Hoefsloot et al., also provides strong evidence regarding the structural and functional elements that were well known in the art.

Additional relevant sections from Van Bree et al., (WO 00/34451, 2000, in IDS):

Page 1: Lines 16-28

BACKGROUND OF THE INVENTION

Like other secretory proteins, lysosomal proteins are synthesized in the endoplasmic reticulum and transported to the Golgi apparatus. However, unlike most other secretory proteins, the lysosomal proteins are not destined for secretion into extracellular fluids but into an intracellular organelle. Within the Golgi, lysosomal proteins undergo special processing to equip them to reach their intracellular destination. Almost all lysosomal proteins undergo a variety of posttranslational modifications, including glycosylation and phosphorylation via the 6' position of a terminal mannose group. The phosphorylated mannose residues are recognized by specific receptors on the inner surface of the Trans Golgi Network. The lysosomal proteins bind via these receptors, and are thereby separated from other secretory proteins. Subsequently, small transport vesicles containing the receptor-bound proteins are pinched off from the

Trans Golgi Network and are targeted to their intracellular destination. See generally Kornfeld, Biochem. Soc. Trans. 18, 367-374 (1990).

Page 7: Lines 26-32

In addition to carbohydrate chain modification, most lysosomal proteins undergo proteolytic processing, in which the first event is removal of the signal peptide. The signal peptide of most lysosomal proteins is cleaved after translocation by signal peptidase after which the proteins become soluble. There is suggestive evidence that the signal peptide of acid α-glucosidase is cleaved after the enzyme has left the RER, but before it has entered the lysosome or the secretory pathway (Wisselaar et al., J. Biol. Chem. 268, 2223-2231(1993)).

Page 8: Lines 15-29

C. Transgene Design

Transgenes are designed to target expression of a recombinant lysosomal protein to the mammary gland of a transgenic nonhuman mammal harboring the transgene. The basic approach entails operably linking an exogenous DNA segment encoding the protein with a signal sequence, a promoter and an enhancer. The DNA segment can be genomic, minigene (genomic with one or more introns omitted), cDNA, a YAC fragment, a chimera of two different lysosomal protein genes, or a hybrid of any of these. Inclusion of genomic sequences generally leads to higher levels of expression. Very high levels of expression might overload the capacity of the mammary gland to perform posttranslation modifications, and secretion of lysosomal proteins. However, the data presented below indicate that substantial posttranslational modification occurs including the formation of mannose 6-phosphate groups, notwithstanding a high expression level in the mg/ml range. Substantial modification means that at least about 10, 25, 50, 75 or 90% of secreted molecules bear at least one mannose 6-phosphate group. Thus, genomic constructs or hybrid cDNA-genomic constructs are generally preferred.

Page 9: Lines 11-23

The promoter and enhancer are from a gene that is exclusively or at least preferentially expressed in the mammary gland (i.e., a mammary-gland specific gene). Preferred genes as a source of promoter and enhancer include β-casein, κ-casein, αSl-casein, αS2-casein, β-lactoglobulin, whey acid protein, and α-lactalbumin. The promoter and enhancer are usually but not always obtained from the same mammary-gland specific gene. This gene is sometimes but not necessarily from the same species of mammal as the mammal into which the transgene is to be expressed. Expression regulation sequences from other species such as those from human genes can also be used. The signal sequence must be capable of directing the secretion of the lysosomal protein from the mammary gland. Suitable signal sequences can be derived from mammalian genes encoding a secreted protein. Surprisingly, the natural signal sequences of lysosomal proteins are suitable, not withstanding that these proteins are normally not secreted but targeted to an intracellular organelle.

Page 21: Lines 22-30

EXAMPLES

Example 1: Construction of Transgenes

(a) cDNA construct

Construction of an expression vector containing cDNA encoding human acid α-glucosidase started with the plasmid p16,8hlf3 (see DeBoer et al. (1991) & (1993), supra). This plasmid includes bovine αS1-casein regulatory sequences. The lactoferrin cDNA insert of the parent plasmid was exchanged for the human acid α-glucosidase cDNA (Hoefsloot et al. EMBO J. 7,1697-1704 (1988)) at the ClaI site and SalI site of the expression cassette as shown in Fig. 1.

Examiner is also including the following sections of **Hoefsloot et al. EMBO J. 7,1697-1704 (1988)**, as evidence to indicate the structural and functional elements including the putative signal sequence of human GAA were well known in the art.

Page 1697, Abstract, paragraph 1:

The encoded protein has a molecular mass of 104.645 kd and starts with a signal peptide. Sites of proteolytic processing are established by identification of N-terminal amino acid sequences of the 110-kd precursor, and the 76-kd and 70-kd mature forms of the enzyme encoded by the cDNA. Interestingly, both amino-terminal and carboxy-terminal processing occurs. Sites of sugar chain attachment are proposed.

Page 1699, column 2, paragraph 2:

The amino acid sequence deduced from the open reading frame from position 220 to position 3073 is shown in Figure 4. Four of the 10 amino acids after the first methionine are basic. These are followed by a stretch of 27 amino acids, 20 of which are hydrophobic. A serine is located in this sequence fulfill the requirements for a signal peptide common to lysosomal and secretory proteins (Watson, 1984).

Page 1701, column 1, paragraph 3:

The unambiguous proof was the identification of the amino-terminal sequences of the 110-kd precursor, the 76- and 70-kd mature forms of acid α-glucosidase, and several tryptic and CNBr peptides in the amino acid sequence deduced from the cDNA clone. These sequences are all encoded in the longest open reading frame, in which only one methionine precedes the amino terminus of the 110-kd precursor. That translation starts, indeed, at this methionine is further indicated by the fact that the ATG codon is flanked by the consensus sequence for translation-initiation sites, and is followed by a putative signal sequence.

Page 1701, column 2, paragraph 4:

Some interesting features concerning the post-translational processing of acid α-glucosidase emerge when the spacing of the sequences coding for the precursor and mature enzyme is considered. The 110-kd amino acid sequence starts 69 amino acids after the first methionine. Since signal peptides are in general not much longer than 30 amino acids (Watson, 1984), the 110-kd precursor isolated from human urine may not be the first *in vivo* precursor. It is likely that some proteolytic processing has occurred after removal of the signal peptide. Indeed, as described by Oude Elferink et al. (1984), the precursor present in human urine is slightly different from the precursor in fibroblasts. The precursor found in fibroblasts might well be the first glycosylated precursor, missing only the signal peptide.

Page 1702, column 2, paragraph 1:

Furthermore, the signal peptide of prosucrase - isomaltase is not cleaved off and serves as a membrane anchor (Hunziker et al., 1986), whereas acid α-glucosidase, like other lysosomal enzymes, loses its signal peptide.

In the light of the above cited disclosures examiner takes the following position: The evidence that replacing the leader sequence of native human GAA with a secretory signal sequence and demonstration of biological activities in said chimeric proteins were well known in the art and also envisaged by Van Bree et al.; especially the native secretion signal sequence (leader sequence) linked to the lysosomal protein coding sequence is replaced with a signal sequence i.e, any signal sequence of interest such as mammary gland specific signal sequences like α-lactalbumin, α-casein, β-casein that can be potentially employed as signal sequences for the expression of human GAA transgene, recovery of the expressed polypeptide and use of purified polypeptide for the treatment of patients having genetic or other deficiency resulting in insufficiency of functional lysosomal GAA enzyme (in pages 3-28; especially pages 7, 9 and 10 page 15; Example 3-4, pages 25-28). Thus, providing evidence that recombinant human GAA comprising heterologous secretion signals wherein native leader sequence has been replaced is correctly processed and biologically active, thus implying unaltered glycosylation and correct processing for the maintenance of biological activity.

Examiner is basing the rejection as per the guidelines in MPEP 2131 [R-1]

TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERYELEMENT OF THE CLAIM

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). >"When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the

structures or compositions within the scope of the claim is known in the prior art." Brown v. 3M, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001) (claim to a system for setting a computer clock to an offset time to address the Year 2000 (Y2K) problem, applicable to records with year date data in "at least one of two-digit, three-digit, or four-digit" representations, was held anticipated by a system that offsets year dates in only two-digit formats). See also MPEP§ 2131.02.< "The identical invention must be shown in as complete detail as is contained in the ... claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ip sissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). Note that, in some circumstances, it is permissible to use multiple references in a 35 U.S.C. 102 rejection. See MPEP § 2131.01.

As per the MPEP 2131 [R-1], each and every element of claim 1 is found either expressly or inherently described in Van Bree et al., (WO 00/34451, 2000, in IDS).

II. In support of their request for the rejection under 35 USC § 103 be withdrawn, Appellants' provide the following arguments:

(2) "The fundamental failings of Van Bree et al are discussed above, those comments are incorporated by reference above. Amalfitano et al also fails to teach the required replacement of the leader sequence of human GAA wih a secretory signal sequence…the Examiner fails to indicate where Amalfitano et al teaches or would have suggested replacing the leader of native human GAA wih secretory siganl sequence, as required by the claims" **(see page 11 of Appellants' Appeal-Brief dated 06/14/10)**.

Reply (2): Appellants' arguments have been considered but are found to be non-persuasive for the following reasons:

Examiner would like to reiterate Appellants' arguments are directed against the references individually. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Examiner continues to hold his position "As per the MPEP 2131 [R-1], each and every element of claim 1 is found either expressly or inherently described in Van Bree et al., (WO 00/34451, 2000, in IDS), i.e., Van Bree et al., clearly and unequivocally disclose the invention as recited in claim 1. Therefore, the cited references indeed render the instant invention obvious over cited prior art, as said references provide the structural elements including an isolated nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to human acid α-glucosidase (GAA), wherein said secretory signal sequence replaces the leader sequence of native human GAA, vectors comprising said polynucleotides and pharmaceutical compositions comprising said vector, motivation and expectation of success (see arguments above for maintaining the 102(b) rejection).

Specifically regarding Amalfitano et al., said reference also provides Teaching, Suggestion and Motivation to generate an Adenoviral construct expressing the human GAA. Appellants' are directed to the following sections Amalfitano et al., specification:

Page 28, lines 6-32:

In more preferred embodiments, the deleted recombinant adenovirus vector carries a transgene encoding a lysosomal acid α-glucosidase (GAA),e.g., to treat Type II GSD including infantile (Pompe disease), juvenile and adult onset forms of the disease. More preferably, the lysosomal acid α-glucosidase is a human lysosomal acid α-glucosidase (hGAA). The transgene may encode either the mature GAA protein (e.g., the 76 kD form) or a GAA precursor (e.g., the 110 kD form). Preferably, the transgene encodes a GAA precursor. The term "GAA" as used herein encompasses mature and precursor GAA proteins as well as modified (e.g., truncated or mutated) GAA proteins that retain biological function (i.e., have at least one biological activity of the native GAA protein, e.g., can hydrolyze glycogen)…

The 28 kb acid α-glucosidase gene on chromosome 17 encodes a 3.6 kb mRNA which produces a 951 amino acid polypeptide (Hoefsloot et al, (1988) EMBO J. 7:1697; Martiniuk et al., (1990) DNA and Cell

Biology 9:85). The nucleotide sequence of a cDNA coding for the polypeptide, as well as the deduced amino acid sequence is provided in Hoefsloot et al (*Id.*). The first 27 amino acids of the polypeptide are typical of a leader sequence of a signal peptide of lysosomal and secretory proteins. The enzyme receives co-translational N-linked glycosylation on the endoplasmic reticulum. It is synthesized as a 110-kDa precursor form, which matures by extensive modification of its glycosylation, and phosphorylation and by proteolytic processing through an approximately 90-kDa endosomal intermediate into the final lysosoma176 and 67 kDa forms (Hoefsloot, (1988) EMBO J. 7:1697; Hoefsloot et al, (1990) Biochem. J. 272: 485).

Page 29, lines 6-32:

The human GAA gene as described by Hoefsloot et al, (1988) EMBO J. 7:1697 and Van Hove et al, (1996) Proc. Natl. Acad. Sci. USA 93:65, includes 5' untranslated sequences. In particular preferred embodiments, the hGAA transgene includes the entire approximately 3.8 kb sequence described by Van Hove et al. Alternatively, the deleted adenoviruses of the present invention may encode more or less of the 5' and 3' untranslated regions of the GAA gene.

Those skilled in the art will appreciate that the heterologous nucleotide sequence(s) are preferably operably associated with the appropriate expression control sequences.

Appellants' further argue (3) "The deficiencies of Van Bree et al and Amalfitano et al are discussed above, those comments being incorporated here by reference. The present invention results, at least in part, from studies designed to test the hypothesis that chimeric lysosomal polypeptides containing an alternative signal peptide could increase the seceretion of lysosomal polypeptides from transduced cells and enhance receptor-mediated uptake of lysosomal polypeptides in tissues. The data presented in the application (and in Sun et al, Mol. Ther. 14:822 (2006) (of record)-a copy of which is submitted herewith) make it clear that replacement of the lysosomal leader sequence (which targets the polypeptide to the lysosome) by secretory signal peptide increased secretion from cultured cells...As discussed above, neither Van Bree et al or Amalfitano et al teach or would have suggested replacement of the leader sequence of native human GAA with a secretory signal sequence. Nothing in the teachings of Heus relating to 3' untranslated regions of GAA or in Haseltine et al's teaching of the albumin signal sequence provide such a teaching or suggestion. Appellants' submit that it is only with

hindsight that the cited references would have been combined..." **(see page 12-13 of Appellants' Appeal-Brief dated 06/14/10)**.

Reply (3): Appellants' arguments have been considered but are found to be non-persuasive for the following reasons:

Examiner would like to reiterate, Appellants' arguments are directed against the references individually. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Moreover, the objectives of the cited references need not be the same as the instant invention to be used in an Obviousness rejection. So long as the motivation or suggestion to combine the teaching of the cited references is known or disclosed in the prior art and is obvious to one skilled in the art. This is sufficient to establish a *prima facie* case of obviousness.

In response to Appellants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellants' disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Specifiaclly reagarding the Applellants' arguments "The data presented in the application (and in Sun et al, Mol. Ther. 14:822 (2006) (of record)-a copy of which is submitted herewith) make it clear that replacement of the lysosomal leader sequence (which targets the polypeptide to the lysosome) by secretory signal peptide increased secretion from cultured cells"; examiner takes the position that Office has provided evidence that establishes "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." KSR, 550 at U.S. 398 (2007), 82 USPQ2d at 1397. All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods **with no change in their respective functions**, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. KSR, 550 U.S. 398 (2007), 82 USPQ2d at 1397; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).

Appellants' further argue (4) "The deficiencies of Van Bree et al and Amalfitano et al are discussed above, those comments being incorporated here by reference. Nothing in the teachings of Heus relating to 3' untranslated regions of GAA or in Haseltine et al's teaching of the albumin siganl sequence or in Martin et al's teaching of an erythropoietin

siganl peptide would have cured the fundamental failings of Van Bree et al and Amalfitano et al. In addition, the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention" **(see page 13 of Appellants' Appeal-Brief dated 06/14/10)**.

Reply (4): Appellants' arguments have been considered but are found to be non-persuasive for the following reasons:

Examiner would like to reiterate, Appellants' arguments are directed against the references individually. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Moreover, the objectives of the cited references need not be the same as the instant invention to be used in an Obviousness rejection. So long as the motivation or suggestion to combine the teaching of the cited references is known or disclosed in the prior art and is obvious to one skilled in the art. This is sufficient to establish a *prima facie* case of obviousness.

In response to Appellants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellants' disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Appellants' further argue (4) "The deficiencies of van Bree et al and Amalfitano et al are discussed above, those comments being incorporated here by reference. Nothing in the teachings of Heus relating to 3' untranslated regions of GAA or in Haseltine et al's teaching of the albumin siganl sequence or in Martin et al's teaching of an erythropoietin siganl peptide would have cured the fundamental failings of Van Bree et al and Amalfitano et al. In addition, the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention" **(see page 13 of Appellants' Appeal-Brief dated 06/14/10)**.

Reply (4): Appellants' arguments have been considered but are found to be non-persuasive for the following reasons:

Examiner would like to reiterate, Appellants' arguments are directed against the references individually. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Moreover, the objectives of the cited references need not be the same as the instant invention to be used in an Obviousness rejection. So long as the motivation or suggestion to combine the teaching of the cited references is known or disclosed in the prior art and is obvious to one skilled in the art. This is sufficient to establish a *prima facie* case of obviousness.

In response to Appellants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellants' disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Appellants' further argue (5) "The failings of Van Bree et al and Amalfitano et al are discussed above, those comments being incorporated here by reference. Nothing in the teachings of Heus relating to 3' untranslated regions of GAA or in Haseltine et al's teaching of the albumin siganl sequence or in Martin et al's teaching of an erythropoietin siganl peptide would have cured those failings, nothing in Whitfeld et al's taechings realting to a therapeutic polypetide comprising an α-1-antitrypsin secretory siganl sequence… Meuelien's teaching of a Factor IX secretory signal sequence certainly would not have provided such a suggestion" **(see page 14 of Appellants' Appeal-Brief dated 06/14/10)**.

Reply (5): Appellants' arguments have been considered but are found to be non-persuasive for the following reasons:

Examiner would like to reitearte, Appellants' arguments are directed against the references individually. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Moreover, the objectives of the cited references need not be the same as the instant invention to be used in an Obviousness rejection. So long as the motivation or suggestion to combine the teaching of the cited references is known or disclosed in the prior art and is obvious to one skilled in the art. This is sufficient to establish a *prima facie* case of obviousness.

Therefore, the examiner continues to hold the position that the combination of the cited references renders the instant invention obvious for the following reasons. One of ordinary skill in the art would have been motivated to make an isolated nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to human acid α-glucosidase (GAA), wherein said secretory signal sequence replaces the leader sequence of native human GAA as taught by Van Bree et al., using the α-glucosidase (GAA) sequence of SEQ ID NO: 2 of Amalfitano et al., as a therapeutic construct configured in an adeno-associated virus vector and pharmaceutical compositions comprising said vector and further modifying said human acid α-glucosidase (GAA) to comprise any heterologous signal sequence of interest as taught by Heus JH, Haseltine et al., Martin et al., and Meulien P. One of ordinary skill in the art would have been motivated to combine these references because those of ordinary skill would have recognized that a chimeric polypeptide comprising a secretory signal sequence operably linked to human acid α-glucosidase (GAA), wherein said secretory signal sequence replaces the leader sequence of native human GAA could be

used for effective targeting of said therapeutic polypeptide to clinically significant target tissues. The expectation of success of merely making an isolated nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to human acid α-glucosidase (GAA), wherein said secretory signal sequence replaces the leader sequence of native human GAA is high, because methods for constructing vectors configured to express human acid α-glucosidase (GAA) comprising heterologous secretory signal sequences were well known in the art as supported by Van Bree et al., Amalfitano et al., and Heus JH.

The basis for the examniner to continue to hold his position is reasoned below; examiner has provided unequivoical evidence for combining the cited references and that the cited references have been properly applied in this obviousness rejection in accordance with the factual enquires set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling. Furthermore the cited references teach all the limitations of the instant claims.

The cited references render claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 *prima facie* obvious to one of ordinary skill in the art when one applies the Teaching, Suggestion and Motivation (TSM) test under the rationale for arriving at a conclusion of obviousness as suggested by the KSR ruling. The rationale applied for this rejection is as follows:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. The instant invention is a simple combination of elements taught in the prior art, wherein the elements of prior art are combined to yield predictable results and the choice is from a finite number of identified elements with a highly predictable outcome and expectation of success.

Examiner has endeavored in his **reply (1)-(5)** above to establish that the cited references are in congruence with the obviousness rejection and teach all limitations of the instant claims i. e., meet all the criteria and parameters (Teaching, Suggestion and Motivation) as defined by *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according

to KSR ruling.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Ganapathirama Raghu/
Patent Examiner
Art Unit 1652

Conferees:
/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645

/JON P WEBER/
Supervisory Patent Examiner, Art Unit 1657